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| EXAMINER | |
|---|---|
| KELLY, ROBERT M | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1633 | |

DATE MAILED: 09/07/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/804,763 | QI ET AL. | |
| | Examiner | Art Unit | |
| | Robert M. Kelly | 1633 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *05 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) *3,4 and 12-17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 5-11* is/are rejected.

7)☒ Claim(s) *9* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 7/22/04; 10/18/04; 2/15/05; 5/22/06
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

Applicant's amendment and response of 5/31/06 is entered.

Claims 8-12 and 14 are amended.

Claims 1-17 are presently pending.

### *Election/Restrictions*

Applicant's election without traverse of Group I, Claims 1-11 and the species of SEQ ID NO: 2 and ornithine carbamoyl transferase in the reply filed on 5/31/06 is acknowledged.

Claims 12-17 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 5/31/06.

Further, because Art was discovered for the claimed invention for sequences matching SEQ ID NO:8, SEQ ID NO: 8 is also rejoined with SEQ ID NO: 2 for analysis.

Hence, Claims 3-4 are withdrawn as being drawn to non-elected species which have not been rejoined.

Claims 1-2 and 5-11 are presently considered for the elected invention and species, with the rejoinder of SEQ ID NO: 2.

### *Amendments to the Claims*

It is noted that Applicant's preliminary amendment of 7/22/04 provided several amendments to the claims, upon which Applicant has further amended in the most recent response of 5/31/06. Therefore, the claim identifiers in the present claim amendments,

identifying various claims as "original" which were previously amended, are not considered proper claim identifiers (e.g., Claims 2-5). However, the claim amendments have been accepted by the Examiner. Applicant is forewarned that future non-compliant amendments will be responded with a notice of non-compliant response.

### *Amendment to the Specification*

It is noted that Applicant's amendment to the specification of 7/22/04 does not properly identify that paragraph 056 and the subsequent table are to be replaced, but only the paragraph. Moreover, it is noted that Applicant has failed to mark up the table to indicate deletion of the line with the term "transferas" in the table. However, for purposes of compact prosecution, and because the Examiner is herein identifying these changes, hence, such does not raise a separate objection to the specification.

Also, Applicant's amendment pre-appends the submitted paper sequence listing to the claims, while proper amendment should be to post-append the sequence listing to the end of the specification text. However, such is not detrimental, because the submitted papers listed the pages of the claims consecutively, after the specification. The Examiner is simply making of record that the sequence listing is post-appended to the body of the specification, to avoid problems with the printers, should this Application issue as a patent.

### *Claim Objections*

Claim 9 objected to because of the following informalities: Claim 9 recites "recombonant herpes virus". Proper spelling of such term is "recombinant herpes virus". Appropriate correction is required.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-2 and 5-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the term "a therapeutic gene of interest". The metes and bounds of this term are not clear, given the balance of the claim language and teachings of the specification. To wit, typically in the art, a gene encompasses the transcriptional and translational regulatory elements which are linked to the protein encoding region in the wild-type cell. However, Applicant has claimed the term "gene" and "encoding" sequence in the same claim, and further claimed that at least one first transcription and translational control element for directing expression of the first and second nucleic acid is also present. However, the Artisan on the one hand, taking gene to mean operably linked elements, that the separately claimed control elements were linked to the first nucleic acid encoding sequence only. On the other hand, if the Artisan were to take gene to mean a coding sequence only, Applicant would appear to be claiming a fusion protein, as a single translational control element would not allow for anything but a fusion protein if both nucleic acids claimed were to be expressed. The Examiner understands the specification not to encompass such fusions, however, Applicant is required to make the claim clear for its metes and bounds. However, for purposes of compact prosecution, the Examiner will consider the claim to encompass two sequences which may be co-expressed, but are separately translated, and to also encompass fusion proteins.

Claim 6 recites the limitation "the intracellular domain of wild-type CD8 [alpha]-chain" in Claim 1. There is insufficient antecedent basis for this limitation in the claim. This would typically be considered a claim objection, however, because it is clear that Applicant is also

claiming CD8 chains from other species, the lack of antecedent basis for "wild-type CD8 [alpha]-chain" makes the claim unclear because the Artisan would not know if Applicant is referring to any species' intracellular domain of the chain, or if they mean that particular species' wild-type alpha chain.

Claims 2 and 5-11 are rejected for depending from a rejected base claim and not overcoming the lack of clarity in such base claim.

### *Claim Rejections - 35 USC § 101*

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-6 and 8 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Applicant's claims are broad, and read on the full-length CD8 alpha chain encoded by the wild-type animal. For example, the cd8-alpha chain with the transmembrane peptide may be the extracellular and transmembrane portions, while the therapeutic gene of interest may be the intracellular region of the CD8 alpha chain.

Amending the claim to recite "isolated" would address the basis of the rejection.

### *Claim Rejections - 35 USC § 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2, 5-6 are rejected under 35 U.S.C. 102(b) as being anticipated by US Pat. No. 5,540,926 to Aruffo, et al., as further evidenced by WO 04/042346 to Wohlgemuth, et al. and that attached SEQUENCE COMPARISON 1 OF 9/6/06.

Aruffo teaches the preparation of soluble GP39, wherein the GP39 is linked to human CD8 which minimally comprises its extracellular domain (e.g., col. 8, paragraph 5). Such proteins are taught to be made from nucleic acids transformed into a host cell which comprises an operatively linked promoter, and inherently must also comprise the transcriptional control elements, otherwise the proteins would not be able to transcribed (e.g., col. 7, paragraph 4).

With regard to claim 8-9, Aruffo also teaches the use of plasmids and adenoviral vectors (col. 7, paragraph 3).

Further, as evidenced by Wohlgemuth, the nucleotide sequence is 100% identical to Applicant's claimed sequence for human CD8 (See Attached SEQUENCE COMPRISON 1 OF 9/6/06, which demonstrates the sequence identity).

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-2, 5-6, and 8-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat. No. 5,540,926 to Aruffo, et al., and US Pat. No. 6,193,980 to Efstathiou, et al., as further evidenced by WO 04/042346 to Wohlgemuth, et al. and that attached SEQUENCE COMPARISON 1 OF 9/6/06.

As shown above, Aruffo teaches the various aspects of each claim. Moreover, Aruffo teaches that the protein may be grown in any mammalian cell (e.g., col. 7, paragraph 3). However, Aruffo does not teach the aspect of using a replication defective herpes virus vector.

On the other hand, Efstathiou teaches replication defective herpes simplex virus comprising heterologous inserts for producing long-term infection and protein production in, *inter alia*, the sensory neurons of the dorsal root ganglia (e.g., col. 1, paragraph 5).

Hence, at the time of invention, it would have been obvious to modify the vectors of Aruffo with the HSV vectors Efstathiou to arrive at the claimed invention. The artisan would have been motivated to do so in order to express the transgene for long terms, in dorsal root ganglia cells. The Artisan would also have had a reasonable expectation of success, Aruffo had demonstrated the protein's production, and Efstathiou had demonstrated that the vectors were useful for protein production in dorsal root ganglia.

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-2, 5-6, and 8-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat. No. 5,540,926 to Aruffo, et al., and US Pat. No. 6,509,150 Salvetti, et al., as further evidenced by WO 04/042346 to Wohlgemuth, et al. and that attached SEQUENCE COMPARISON 1 OF 9/6/06.

As shown above, Aruffo teaches the various aspects of each claim. Moreover, Aruffo teaches that the protein may be grown in any mammalian cell (e.g., col. 7, paragraph 3). However, Aruffo does not teach the aspect of using a replication defective herpes virus vector.

On the other hand, Salvetti teaches adenoassociated viral vectors comprising heterologous inserts with improved efficiency, and may be for specific localization of intergration of the vector (ABSTRACT; col. 6, last paragraph).

Hence, at the time of invention, it would have been obvious to modify the vectors of Aruffo with the AAV vectors of Salvetti to arrive at the claimed invention. The artisan would have been motivated to do so in order to produce vectors with improved efficiency, for producing pharmaceutical proteins. The Artisan would also have had a reasonable expectation of success, Aruffo had demonstrated the protein's production, and Salvetti had demonstrated that the vectors could be used for specific integration (EXAMPLES).

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

> having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-2, 5-6, 8, and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat. No. 5,540,926 to Aruffo, et al., and US Pat. No. 6,207,456 to Baru, et al., as further evidenced by WO 04/042346 to Wohlgemuth, et al. and that attached SEQUENCE COMPARISON 1 OF 9/6/06.

As shown above, Aruffo teaches the various aspects of each claim. Moreover, Aruffo teaches that the protein may be grown in any mammalian cell (e.g., col. 7, paragraph 3). However, Aruffo does not teach the aspect of using a replication defective herpes virus vector.

On the other hand, Baru teaches liposome delivery systems for plasmids comprising heterologous inserts with improved efficiency in vitro (e.g., ABSTRACT; col. 1, last paragraph).

Hence, at the time of invention, it would have been obvious to modify the plasmid vectors of Aruffo with the liposome vectors of Baru to arrive at the claimed invention. The artisan would have been motivated to do so in order to produce vectors with improved efficiency, for producing pharmaceutical proteins. The Artisan would also have had a reasonable expectation of success, Aruffo had demonstrated the protein's production, and Baru had demonstrated the improved efficiency of such vector liposomes (EXAMPLES).

### *Claim Rejections - 35 USC § 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3-6, 8-9, and 10 are rejected under 35 U.S.C. 102(b) as being anticipated by Bonyhadi, et al. (1997) J. Virol., 71(6): 4707-16.

With regard to Claim 1 and 3-5, Bonyhadi teaches a nucleotide sequence comprising both a sequence encoding a therapeutic Rev mutant, and the mouse CD8-alpha gene sequence (e.g., FIGURE 2). Moreover, such sequences are operably linked to one or more transcriptional and translational regulatory sequences for their expression (e.g., the LTR and and an IRES). Because the gene is the mouse sequence for CD8-alpha, absent reason to believe otherwise, such sequence matches SEQ ID NO: 8, and/or is 80% similar to SEQ ID NO: 8.

With regard to Claim 6, the CD8 used lacks the cytoplasmic tail (p. 4708, col. 2, paragraph 2).

With regard to Claims 8-9, the viral vector in which this contruct is placed is an MMLV retroviral vector (Id.).

With regard to Claim 10, the viral vector is defective for replication, lacking all replication gene expression, and only the LTR is active (FIGURE 2), and requiring a packing cell line for production of virus (p. 4708, col. 1, paragraph 2).

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3-7 and 5-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zimmer, et al. (1999) Molecular Medicine 5(4): 244-53 and Bonyhadi, et al. (1997) J. Virol., 71(6): 4707-16.

Zimmer teaches the administration of adenoviral vectors comprising the mouse or human ornithine carbamoyl transferase gene, for treatment of mice with OTC deficiency (ABSTRACT).

However, Zimmer does not teach the aspects of such adenoviral vector further comprising a CD8-alpha transgene.

On the other hand, Bonyhadi teaches that a second transgene encoding for CD8-alpha chain can be used for detection and/or enrichment of the transformation of the transduced cells (p. 4708, paragraph bridging columns). Further, as noted above, the CD8-alpha gene meets the requirements of Claims 1 and 3-6.

Hence, at the time of filing it would have been obvious to modify the methods of Zimmer with those of Bonyhadi, to arrive at an adenoviral vector comprising transgenes for CD8-alpha, lacking its cytoplasmic tail, and for ornithine carbamoyl transferase. The Artisan would be motivated to do so to monitor and isolate the cells of Zimmer's transformed animals that were transformed, in order to study the amounts of ornithine carbamoyl transferase which was expressed, as taught by Zimmer. Moreover, the Artisan would have had a reasonable expectation of success, Zimmer had shown the method to work, and Bonyhadi had demonstrated that the cells' protein levels could be analyzed.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Zimmer, et al. (1999) Molecular Medicine 5(4): 244-53 and Bonyhadi, et al. (1997) J. Virol., 71(6): 4707-16 as applied to claims 1, 3-7 and 5-9 above, and further in view of Liang, et al. (2002) Gene Therapy, 9: 1659-66.

As shown above, Zimmer and Bonyhadi alone make Claims 1, 3-7, and 5-9 obvious, however, they do not teach or suggest the aspect of using a replication-defective adenovirus.

On the other hand, Liang teaches methods of monitoring adenovirus DNA delivery, using a replication-defective adenovirus (ABSTRACT).

Hence, at the time of invention by Applicant, it would have been obvious to modify the methods of Zimmer and Bonyhadi with that of Liang, and use a replication defective adenoviral vector. The Artisan would have been motivated to do so because Liang had demonstrated that such replication-defective adenoviral vectors were equally able to be used when monitoring was required. Moreover, the Artisan would have had a reasonable expectation of success, as Zimmer and Bonyhadi had demonstrated the method would work, and Liang had demonstrated that replication defective adenoviral vectors could be used in such methods.

***Conclusion***

No Claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert M. Kelly, Art Unit 1633, whose telephone number is (571) 272-0729. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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